

FILE 'HOME' ENTERED AT 17:02:22 ON 13 MAR 2007

=> file registry

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.21

FILE 'REGISTRY' ENTERED AT 17:03:03 ON 13 MAR 2007

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 12 MAR 2007 HIGHEST RN 926069-79-6

DICTIONARY FILE UPDATES: 12 MAR 2007 HIGHEST RN 926069-79-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

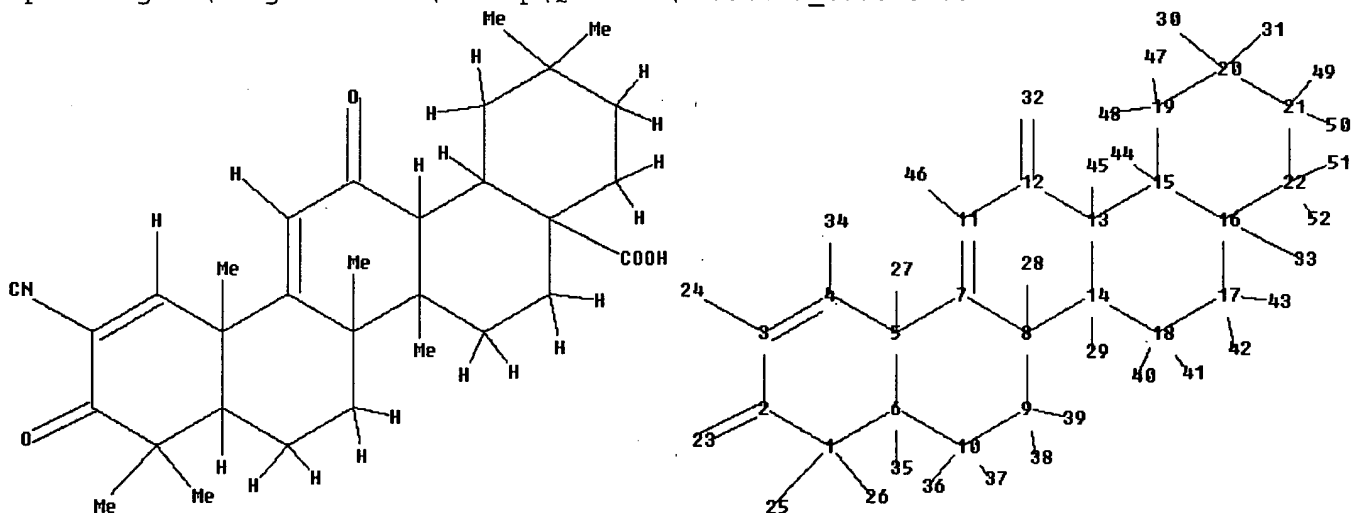
Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

=>

Uploading C:\Program Files\Stnexp\Queries\09998009_cddome.str



chain nodes :

23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43
44 45 46 47 48 49 50 51 52

ring nodes :

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

chain bonds :

1-25 1-26 2-23 3-24 4-34 5-27 6-35 8-28 9-38 9-39 10-36 10-37 11-46

12-32 13-45 14-29 15-44 16-33 17-42 17-43 18-40 18-41 19-47 19-48 20-30
 20-31 21-49 21-50
 22-51 22-52
 ring bonds :
 1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 7-11 8-9 8-14 9-10 11-12 12-13
 13-14 13-15 14-18 15-16 15-19 16-17 16-22 17-18 19-20 20-21 21-22
 exact/norm bonds :
 1-2 1-6 2-3 2-23 3-4 4-5 5-6 5-7 6-10 7-8 7-11 8-9 8-14 9-10 11-12
 12-13 12-32 13-14 13-15 14-18 15-16 15-19 16-17 16-22 17-18 19-20 20-21
 21-22
 exact bonds :
 1-25 1-26 3-24 4-34 5-27 6-35 8-28 9-38 9-39 10-36 10-37 11-46 13-45
 14-29 15-44 16-33 17-42 17-43 18-40 18-41 19-47 19-48 20-30 20-31 21-49
 21-50 22-51
 22-52

Match level :

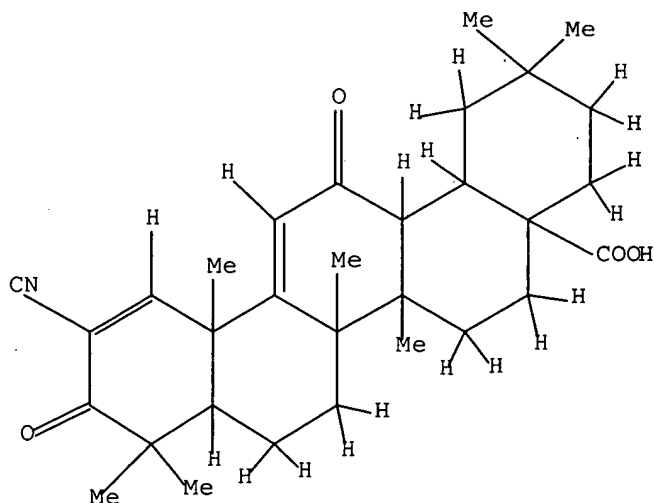
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 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
 20:Atom 21:Atom
 22:Atom 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS
 30:CLASS 31:CLASS
 32:CLASS 33:CLASS 34:CLASS 35:CLASS 36:CLASS 37:CLASS 38:CLASS 39:CLASS
 40:CLASS 41:CLASS
 42:CLASS 43:CLASS 44:CLASS 45:CLASS 46:CLASS 47:CLASS 48:CLASS 49:CLASS
 50:CLASS 51:CLASS
 52:CLASS

L1 STRUCTURE UPLOADED

=> d 11

L1 HAS NO ANSWERS

L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s 11.exa full

FULL SEARCH INITIATED 17:03:28 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 20 TO ITERATE

100.0% PROCESSED 20 ITERATIONS

1 ANSWERS

SEARCH TIME: 00.00.01

L2 1 SEA EXA FUL L1

=> d 12

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN

RN 218600-44-3 REGISTRY

ED Entered STN: 29 Jan 1999

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN 2-Cyano-3,12-dioxooleana-1,9-dien-28-oic acid

CN CDDO

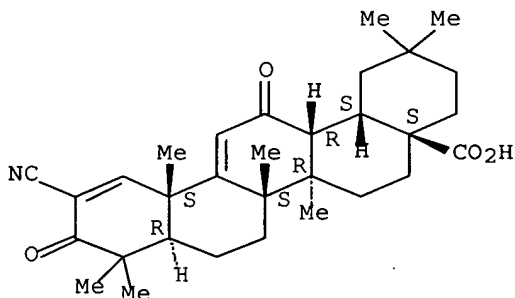
FS STEREOSEARCH

MF C31 H41 N O4

SR CA

LC STN Files: CA, CAPLUS, CASREACT, IMSDRUGNEWS, IMSRESEARCH, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

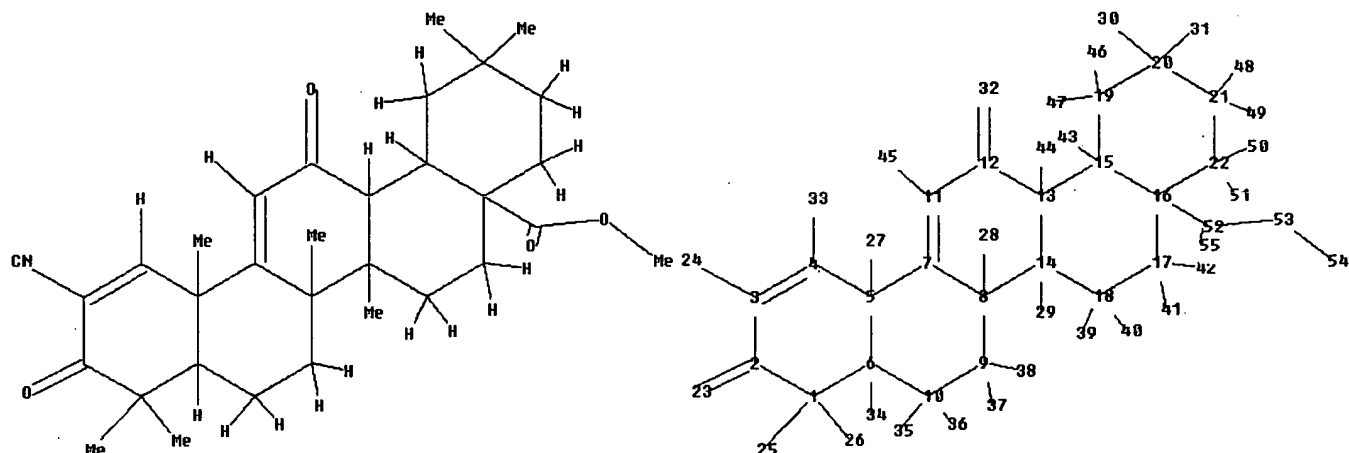
48 REFERENCES IN FILE CA (1907 TO DATE)

2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

48 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

Uploading C:\Program Files\Stnexp\Queries\09998009_cddome_2.str



chain nodes :

23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43
44 45 46 47 48 49 50 51 52 53 54 55

ring nodes :

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

chain bonds :

1-25 1-26 2-23 3-24 4-33 5-27 6-34 8-28 9-37 9-38 10-35 10-36 11-45
12-32 13-44 14-29 15-43 16-52 17-41 17-42 18-39 18-40 19-46 19-47 20-30
20-31 21-48 21-49
22-50 22-51 52-53 52-55 53-54

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 7-11 8-9 8-14 9-10 11-12 12-13
13-14 13-15 14-18 15-16 15-19 16-17 16-22 17-18 19-20 20-21 21-22

exact/norm bonds :

1-2 1-6 2-3 2-23 3-4 4-5 5-6 5-7 6-10 7-8 7-11 8-9 8-14 9-10 11-12
12-13 12-32 13-14 13-15 14-18 15-16 15-19 16-17 16-22 17-18 19-20 20-21
21-22 52-53
52-55

exact bonds :

1-25 1-26 3-24 4-33 5-27 6-34 8-28 9-37 9-38 10-35 10-36 11-45 13-44
14-29 15-43 16-52 17-41 17-42 18-39 18-40 19-46 19-47 20-30 20-31 21-48
21-49 22-50
22-51 53-54

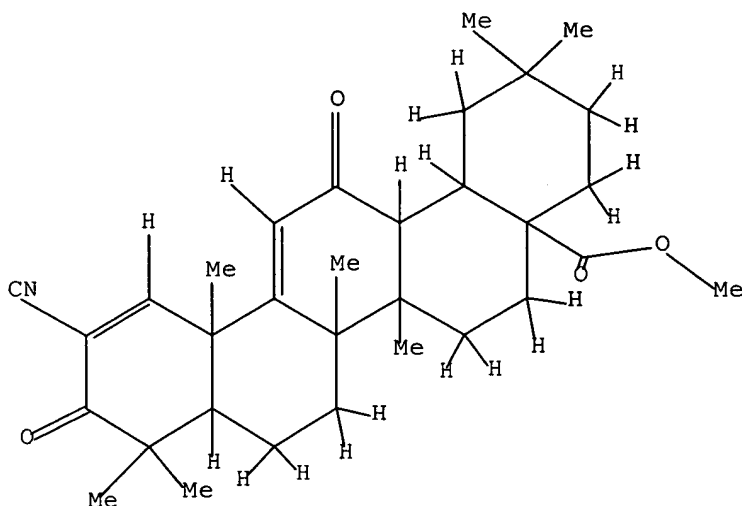
Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
20:Atom 21:Atom
22:Atom 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS
30:CLASS 31:CLASS
32:CLASS 33:CLASS 34:CLASS 35:CLASS 36:CLASS 37:CLASS 38:CLASS 39:CLASS
40:CLASS 41:CLASS
42:CLASS 43:CLASS 44:CLASS 45:CLASS 46:CLASS 47:CLASS 48:CLASS 49:CLASS
50:CLASS 51:CLASS
52:CLASS 53:CLASS 54:CLASS 55:CLASS

L3 STRUCTURE UPLOADED

=> d 13

L3 HAS NO ANSWERS
L3 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l3 exa full

FULL SEARCH INITIATED 17:06:33 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 20 TO ITERATE

100.0% PROCESSED 20 ITERATIONS

1 ANSWERS

SEARCH TIME: 00.00.01

L4 1 SEA EXA FUL L3

=> d l4

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN

RN 218600-53-4 REGISTRY

ED Entered STN: 29 Jan 1999

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

FS STEREOSEARCH

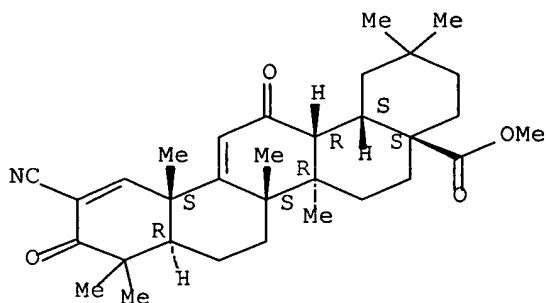
MF C32 H43 N O4

CI COM

SR CA

LC STN Files: CA, CAPLUS, CASREACT, IMSDRUGNEWS, IMSRESEARCH, PROUSDDR,
SYNTHLINE, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

20 REFERENCES IN FILE CA (1907 TO DATE)
20 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file medline, caplus, wpids, uspatfull

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

122.20

122.41

FILE 'MEDLINE' ENTERED AT 17:06:49 ON 13 MAR 2007

FILE 'CAPLUS' ENTERED AT 17:06:49 ON 13 MAR 2007

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE 'WPIDS' ENTERED AT 17:06:49 ON 13 MAR 2007

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FILE 'USPATFULL' ENTERED AT 17:06:49 ON 13 MAR 2007

CA INDEXING COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

=> s 14

SAMPLE SEARCH INITIATED 17:06:54 FILE 'WPIDS'

SAMPLE SCREEN SEARCH COMPLETED - 0 TO ITERATE

100.0% PROCESSED

0 ITERATIONS

0 ANSWERS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**

BATCH **COMPLETE**

PROJECTED ITERATIONS: 0 TO 0

PROJECTED ANSWERS: 0 TO 0

L5 25 L4

=> s 15 not py>2000

L6 3 L5 NOT PY>2000

=> d 16 1-3 ibib, abs, hitstr

L6 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:702718 CAPLUS Full-text
DOCUMENT NUMBER: 134:274
TITLE: A synthetic triterpenoid, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO), is a ligand for the peroxisome proliferator-activated receptor γ
AUTHOR(S): Wang, Yongping; Porter, Weston W.; Suh, Nanjoo; Honda, Tadashi; Gribble, Gordon W.; Leesnitzer, Lisa M.; Plunket, Kelli D.; Mangelsdorf, David J.; Blanchard, Steven G.; Willson, Timothy M.; Sporn, Michael B.
CORPORATE SOURCE: Department of Pharmacology, Dartmouth Medical School and Dartmouth College, Hanover, NH, 03755, USA
SOURCE: Molecular Endocrinology (2000), 14(10), 1550-1556
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

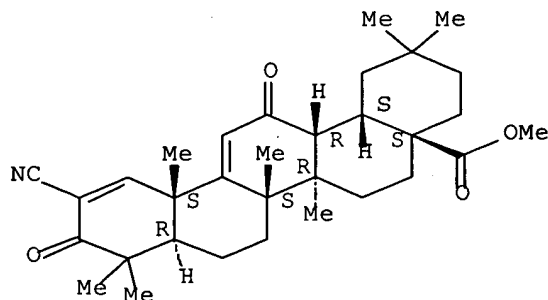
AB A novel synthetic triterpenoid, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO), previously reported to have potent differentiating, antiproliferative, and antiinflammatory activities, has been identified as a ligand for the peroxisome proliferator-activated receptor γ (PPAR γ). CDDO induces adipocytic differentiation in 3T3-L1 cells, although it is not as potent as the full agonist of PPAR γ , rosiglitazone. Binding studies of CDDO to PPAR γ using a scintillation proximity assay give a K_i between 10^{-8} to 10^{-7} M. In transactivation assays, CDDO is a partial agonist for PPAR γ . The Me ester of CDDO, CDDO-Me, binds to PPAR γ with similar affinity, but is an antagonist. Like other PPAR γ ligands, CDDO synergizes with a retinoid X receptor (RXR)-specific ligand to induce 3T3-L1 differentiation, while CDDO-Me is an antagonist in this assay. The partial agonism of CDDO and the antagonism of CDDO-Me reflect the differences in their capacity to recruit or displace cofactors of transcriptional regulation; CDDO and rosiglitazone both release the nuclear receptor corepressor, NCoR, from PPAR γ , while CDDO-Me does not. The differences between CDDO and rosiglitazone as either partial or full agonists, resp., are seen in the weaker ability of CDDO to recruit the coactivator CREB-binding protein, CBP, to PPAR γ . Our results establish the triterpenoid CDDO as a member of a new class of PPAR γ ligands.

IT 218600-53-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(synthetic triterpenoid, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO): ligand for PPAR γ)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:632697 CAPLUS Full-text

DOCUMENT NUMBER: 133:350364

TITLE: Synthetic Oleanane and Ursane Triterpenoids with Modified Rings A and C: A Series of Highly Active Inhibitors of Nitric Oxide Production in Mouse Macrophages

AUTHOR(S): Honda, Tadashi; Rounds, BarbieAnn V.; Bore, Lothar; Finlay, Heather J.; Favalaro, Frank G. ,Jr.; Suh, Nanjoo; Wang, Yongping; Sporn, Michael B.; Gribble, Gordon W.

CORPORATE SOURCE: Department of Chemistry, Dartmouth College Dartmouth Medical School, Hanover, NH, 03755, USA

SOURCE: Journal of Medicinal Chemistry (2000), 43(22), 4233-4246

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 133:350364

AB New olean- and urs-1-en-3-one triterpenoids with various modified rings C have been synthesized as potential antiinflammatory and cancer chemopreventive agents and evaluated for their inhibitory activities against production of nitric oxide induced by interferon- γ in mouse macrophages. These studies revealed that 9(11)-en-12-one and 12-en-11-one functionalities in ring C increase the potency by about 2-10 times compared with the original 12-ene. Subsequently, novel olean- and urs-1-en-3-one derivs. with nitrile and carboxyl groups at C-2 in ring A and with 9(11)-en-12-one and 12-en-11-one functionalities in ring C were synthesized. Among them, Me 2-cyano-3, 12-dioxooleana-1,9(11)-dien-28-oate, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) (I), and Me 2-carboxy-3,12-dioxooleana-1,9(11)-dien-28-oate were found to have extremely high potency ($IC_{50} = 0.1$ nM level). Their potency is similar to that of dexamethasone although they do not act through the glucocorticoid receptor. Overall, the combination of modified rings A and C increases the potency by about 10 000 times compared with the lead compound, 3-oxooleana-1,12-dien-28-oic acid ($IC_{50} = 1$ μ M level). The selected oleanane triterpenoid, I, was found to be a potent, multifunctional agent in various in vitro assays and to show antiinflammatory activity against thioglycollate-interferon- γ -induced mouse peritonitis.

IT 218600-53-4P

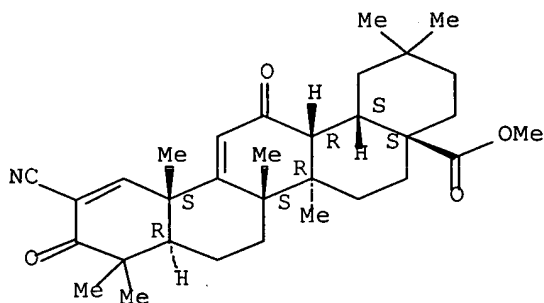
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)

(synthetic oleanane and ursane triterpenoids, a series of highly active inhibitors of nitric oxide production in mouse macrophages)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 1998:709911 CAPLUS Full-text
 DOCUMENT NUMBER: 130:75734

TITLE: Design and synthesis of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, a novel and highly active inhibitor of nitric oxide production in mouse macrophages
 AUTHOR(S): Honda, Tadashi; Rounds, BarbieAnn V.; Gribble, Gordon W.; Suh, Nanjoo; Wang, Yongping; Sporn, Michael B.

CORPORATE SOURCE: Department of Chemistry, Dartmouth College, Hanover, NH, 03755, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (1998), 8(19), 2711-2714
 CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 130:75734

AB New derivs. with electron-withdrawing substituents at the C-2 position of 3-oxoolean-1-en-28-oic acid were synthesized. Among them, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) was 400 times more potent than previous compds. the authors have made as an inhibitor of production of nitric oxide induced by interferon- γ in mouse macrophages (IC₅₀, 0.4 nM). Structure-activity relations are discussed. The potency of CDDO was similar to that of dexamethasone, although CDDO does not act through the glucocorticoid receptor.

IT 218600-53-4P

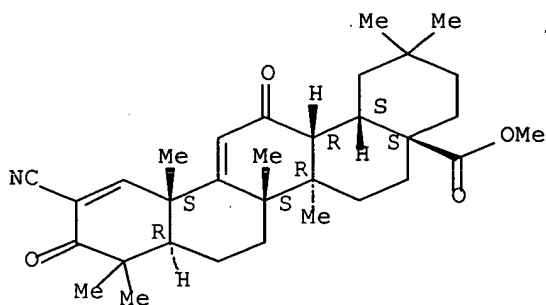
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; design and synthesis of 2-cyanodioxooleandienoic acid as novel and highly active inhibitor of nitric oxide production in mouse macrophages in relation to structure)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d 15 1-25 ibib, abs, hitstr

L5 ANSWER 1 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:1220460 CAPLUS Full-text

DOCUMENT NUMBER: 146:134811

TITLE: Triterpenoid CDDO-Me blocks the NF- κ B pathway by direct inhibition of IKK β on cys-179

AUTHOR(S): Ahmad, Rehan; Raina, Deepak; Meyer, Colin; Kharbanda, Surender; Kufe, Donald

CORPORATE SOURCE: Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115, USA

SOURCE: Journal of Biological Chemistry (2006), 281(47), 35764-35769

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The novel oleanane triterpenoid 2-cyano-3,12-dioxooleana-1,9,-dien-28-oic acid (CDDO) and the C-28 Me ester (CDDO-Me) induce apoptosis of human tumor cells by disruption of redox balance and are currently in clin. trials. The present studies show that CDDO and CDDO-Me block tumor necrosis factor α -induced targeting of NF- κ B p65 to the nucleus. CDDO-Me also blocked tumor necrosis factor α -induced phosphorylation of I κ B α . In concert with these results, we found that CDDO-Me inhibits I κ B α kinase β (IKK β) activity in cells. In support of a direct mechanism, CDDO-Me inhibited recombinant IKK β activity in vitro. The results also demonstrate that (i) CDDO and CDDO-Me form adducts with IKK β , but not IKK β with mutation of Cys-179 to Ala, and (ii) CDDO-Me inhibits IKK β by a mechanism dependent on oxidation of Cys-179. These findings indicate that CDDO and CDDO-Me directly block IKK β activity and thereby the NF- κ B pathway by interacting with Cys-179 in the IKK β activation loop.

IT 218600-53-4

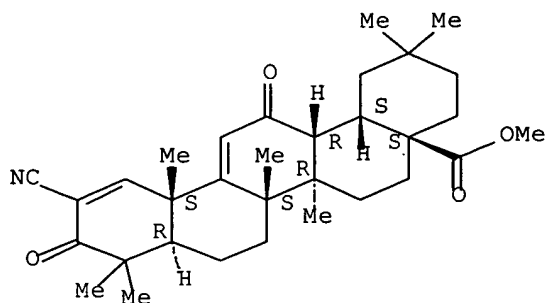
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(triterpenoid CDDO-Me blocks NF- κ B pathway by direct inhibition of IKK β on cys-179)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:823024 CAPLUS Full-text

DOCUMENT NUMBER: 146:220301

TITLE: Depletion of intracellular glutathione contributes to JNK-mediated death receptor 5 upregulation and apoptosis induction by the novel synthetic triterpenoid methyl-2-cyano-3, 12-dioxooleana-1, 9-dien-28-oate (CDDO-Me)

AUTHOR(S): Yue, Ping; Zhou, Zhongmei; Khuri, Fadlo R.; Sun, Shi-Yong

CORPORATE SOURCE: Department of Hematology and Oncology; Winship Cancer Institute; Emory University of School of Medicine, Atlanta, GA, USA

SOURCE: Cancer Biology & Therapy (2006), 5(5), 492-497
CODEN: CBTAAO; ISSN: 1538-4047

PUBLISHER: Landes Bioscience

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The novel synthetic triterpenoid methyl-2-cyano-3, 12-dioxooleana-1, 9-dien-28-oate (CDDO-Me) induces apoptosis in human cancer cells, showing potential as a cancer therapeutic agent. We previously demonstrated that CDDO-Me induces a c-Jun N-terminal kinase (JNK)-mediated DR5 expression and apoptosis. This study revealed the mechanism by which CDDO-Me induces JNK activation and subsequent DR5 upregulation and apoptosis. To determine whether CDDO-Me activates JNK and induces DR5 expression and apoptosis via oxidative stress by inducing the generation of reactive oxygen species (ROS), we examined the effects of various antioxidants on JNK activation, DR5 upregulation, and apoptosis induction by CDDO-Me. Thiol antioxidants, including N-acetyl-L-cysteine (NAC), glutathione (GSH) and dithiothreitol (DTT), abrogated CDDO-Me-induced apoptosis. In contrast, nonthiol antioxidants, including butylated hydroxyanisole (BHA), Trolox, mannitol, and Mn(II) tetra(4-benzoic acid) porphyrin chloride (MnTBAP), failed to do so, with the exception of vitamin C (Vit C). Accordingly, only thiol antioxidants blocked JNK activation induced by CDDO-Me. CDDO-Me reduced intracellular levels of GSH; this reduction was abrogated only by thiol antioxidants and Vit C. However, CDDO-Me did not promote ROS generation. These results suggest that depletion of intracellular GSH, but not ROS generation, contributes to CDDO-Me-induced JNK activation and apoptosis, at least in our systems. Furthermore, these thiol antioxidants abrogated CDDO-Me-induced DR5 expression, whereas the GSH-depleting agent

diethylmaleate also upregulated DR5 expression at concns. that deplete intracellular GSH, demonstrating that GSH depletion can cause DR5 upregulation. Collectively, we conclude that CDDO-Me activates the JNK pathway via depletion of intracellular GSH, leading to DR5 upregulation and induction of apoptosis.

IT 218600-53-4

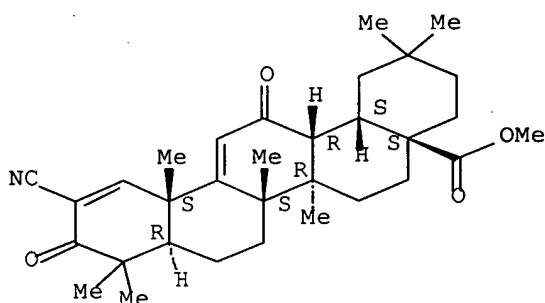
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(glutathione depletion contributes to JNK-mediated death receptor 5 upregulation and apoptosis induction by triterpenoid methyl-2-cyano-3,12-dioxooleana-1,9-dien-28-oate)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:336454 CAPLUS Full-text

DOCUMENT NUMBER: 144:480986

TITLE: A novel mechanism of action of methyl-2-cyano-3,12-dioxoolean-1,9 diene-28-oate: direct permeabilization of the inner mitochondrial membrane to inhibit electron transport and induce apoptosis.

AUTHOR(S): Samudio, Ismael; Konopleva, Marina; Pelicano, Helene; Huang, Peng; Frolova, Olga; Bornmann, William; Ying, Yunming; Evans, Randall; Contractor, Rooha; Andreeff, Michael

CORPORATE SOURCE: Section of Molecular Hematology and Therapy, Departments of Blood and Marrow Transplantation, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

SOURCE: Molecular Pharmacology (2006), 69(4), 1182-1193

CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Methyl-2-cyano-3,12 dioxoolean-1,9 diene-28-oate (CDDO-Me) is a synthetic oleanolic acid derivative that displays antitumorigenic and anti-inflammatory activities, and we have previously reported that this agent potently activates the intrinsic apoptotic pathway in leukemia cells. In this study, we

demonstrate that mitochondrial dysfunction induced by CDDO-Me is mediated by direct permeabilization of the inner mitochondrial membrane, which results in the rapid depletion of mitochondrial glutathione (GSXm), loss of cardiolipin, and inhibition of mitochondrial respiration. More importantly, we demonstrate that in addition to activating the intrinsic apoptotic pathway, the mitochondrial effects of CDDO-Me may mediate its anti-inflammatory activity by modulating the generation of superoxide anion ($O\cdot^-2$). It is noteworthy that CDDO-Me did not increase the generation of $O\cdot^-2$, and pretreatment of leukemia cells with CDDO-Me prevented the increase of this reactive oxygen species elicited by inhibition of complex I or III in the absence of de novo protein synthesis. CDDO-Me, but not other inhibitors of respiration, induced a time- and dose-dependent, cyclosporin A-independent permeability transition (PT) of isolated mitochondria that was sensitive to sulfhydryl antioxidants but not to EDTA. PT induced by CDDO-Me and Ca^{2+} was accompanied by loss of GSXm, suggesting that the increased permeability of the inner mitochondrial membrane facilitates the loss of this antioxidant. Finally, transmission electron microscopy revealed that CDDO-Me rapidly induced caspase-independent mitochondrial swelling and loss of inner membrane structure before the release of cytochrome c. Taken together, our results indicate that CDDO-Me is a novel mitochondriotoxic agent that induces apoptosis and inhibits mitochondrial electron transport via perturbations in inner mitochondrial membrane integrity.

IT 218600-53-4

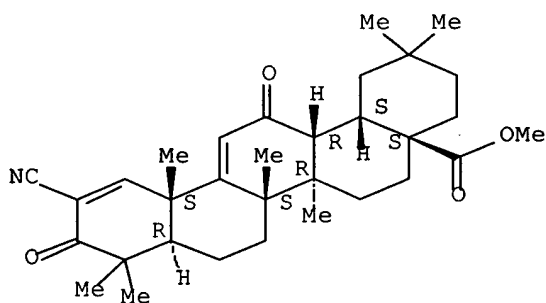
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(methylcyanodioxoolean dieneoate direct permeabilization of inner mitochondrial membrane to inhibit electron transport and induce apoptosis)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:264028 CAPLUS Full-text

DOCUMENT NUMBER: 145:262581

TITLE: A Synthetic Triterpenoid, CDDO-Me, Inhibits
I κ B α Kinase and Enhances Apoptosis Induced
by TNF and Chemotherapeutic Agents through
Down-Regulation of Expression of Nuclear Factor
kB-Regulated Gene Products in Human Leukemic

Cells

AUTHOR(S): Shishodia, Shishir; Sethi, Gautam; Konopleva, Marina; Andreeff, Michael; Aggarwal, Bharat B.

CORPORATE SOURCE: Cytokine Research Laboratory, Department of Experimental Therapeutics and Section of Molecular Hematology and Therapy, Department of Blood and Marrow Transplantation, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

SOURCE: Clinical Cancer Research (2006), 12(6), 1828-1838
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

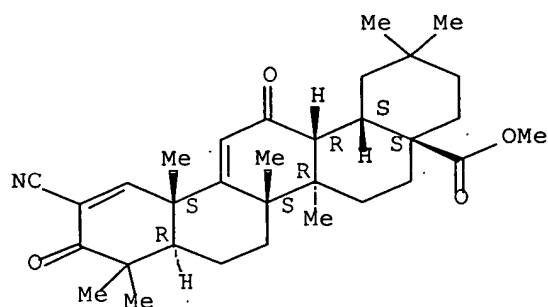
AB The C-28 Me ester of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO-Me), a synthetic triterpenoid based on naturally occurring ursolic and oleanolic acids, induces apoptosis in tumor cells, induces differentiation, and inhibits inflammatory response through a poorly understood mechanism. Because the nuclear transcription factor nuclear factor κ B (NF- κ B) has been shown to suppress apoptosis and promote proliferation and is linked with inflammation and differentiation, we postulated that CDDO-Me modulates NF- κ B activity and NF- κ B-regulated gene expression. Using human leukemia cell lines and patient samples, we show that CDDO-Me potently inhibits both constitutive and inducible NF- κ B activated by tumor necrosis factor (TNF), interleukin (IL)-1 β , phorbol ester, okadaic acid, hydrogen peroxide, lipopolysaccharide, and cigarette smoke. CDDO-Me was more potent than CDDO and its imidazole derivative NF- κ B suppression occurred through inhibition of I κ B α kinase activation, I κ B α phosphorylation, I κ B α degradation, p65 phosphorylation, p65 nuclear translocation, and NF- κ B-mediated reporter gene transcription. This inhibition correlated with suppression of NF- κ B-dependent genes involved in antiapoptosis (IAP2, cFLIP, TRAF1, survivin, and bcl-2), proliferation (cyclin d1 and c-myc), and angiogenesis (VEGF, cox-2, and mmp-9). CDDO-Me also potentiated the cytotoxic effects of TNF and chemotherapeutic agents. Overall, our results suggest that CDDO-Me inhibits NF- κ B through inhibition of I κ B α kinase, leading to the suppression of expression of NF- κ B-regulated gene products and enhancement of apoptosis induced by TNF and chemotherapeutic agents.

IT 218600-53-4
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthetic triterpenoid CDDO-Me inhibited I κ B α kinase and enhanced apoptosis induced by TNF and chemotherapeutic agents through down-regulation of expression of nuclear factor κ B-regulated gene products in human leukemic cell line)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:630016 CAPLUS Full-text

DOCUMENT NUMBER: 143:415675

TITLE: The novel triterpenoid CDDO-Me suppresses MAPK pathways and promotes p38 activation in acute myeloid leukemia cells

AUTHOR(S): Konopleva, M.; Contractor, R.; Kurinna, S. M.; Chen, W.; Andreeff, M.; Ruvolo, P. P.

CORPORATE SOURCE: Section of Molecular Hematology and Therapy, Department of Blood and Marrow Transplantation, The University of Texas MD Anderson Cancer Center, Houston, TX, 77030, USA

SOURCE: Leukemia (2005), 19(8), 1350-1354
CODEN: LEUKED; ISSN: 0887-6924

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Development of novel therapeutic strategies is a continuing challenge for the treatment of acute myeloid leukemia (AML). The novel triterpenoid, C-28 Me ester of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO-Me), induces apoptosis in myeloid leukemic cell lines and in primary AML samples. In this report, the effects of CDDO-Me on CD34+ AML progenitor cells in vitro were examined. CDDO-Me induced apoptosis in all but one of ten AML samples. CDDO-Me is known to inhibit the activation of ERK1/2. In this series of primary AML samples, ERK was expressed and phosphorylated in all patient samples studied and CDDO-Me inhibited ERK phosphorylation in five of 10 samples. However, CDDO-Me induced apoptosis in four of five samples without decreasing pERK levels, suggesting that pERK is not the sole target of the compound. CDDO-Me induced phosphorylation of p38 in AML-derived U937 cells. Pretreatment of U937 cells with a p38 inhibitor protected cells from the cytotoxic effects of CDDO-Me. These findings suggest a role for p38 in CDDO-Me-induced apoptosis. In preliminary studies, CDDO-Me induced p38 phosphorylation in seven of eight primary AML samples. These findings suggest that CDDO-Me treatment shifts cell signaling away from cytoprotective pathways and thus CDDO-Me may be effective for the treatment of AML.

IT 218600-53-4

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

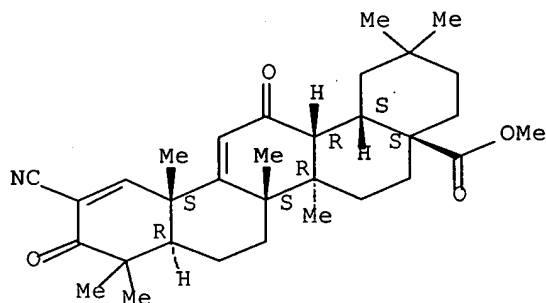
(CDDO-Me induced apoptosis by suppressing ERK phosphorylation in CD34+ acute myeloid leukemia blast cells)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)

(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:580980 CAPLUS Full-text

DOCUMENT NUMBER: 143:221979

TITLE: 2-Cyano-3,12-dioxolean-1,9-dien-28-oic acid and related compounds inhibit growth of colon cancer cells through peroxisome proliferator-activated receptor γ -dependent and -independent pathways

AUTHOR(S): Chintharlapalli, Sudhakar; Papineni, Sabitha; Konopleva, Marina; Andreef, Michael; Samudio, Ismael; Safe, Stephen

CORPORATE SOURCE: Department of Biochemistry and Biophysics, Texas A and M University, College Station, TX, USA

SOURCE: Molecular Pharmacology (2005), 68(1), 119-128
CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 2-Cyano-3,12-dioxolean-1,9-dien-28-oic acid (CDDO) and the corresponding Me (CDDO-Me) and imidazole (CDDO-Im) esters induce peroxisome proliferator-activated receptor γ (PPAR γ)-dependent transactivation in SW-480 colon cancer cells, and these responses were inhibited by small inhibitory RNA for PPAR γ . Moreover, in a mammalian two-hybrid assay using the PPAR γ 2-VP16 fusion plasmid and GAL4-coactivator/corepressor chimeras and a construct (pGAL4) containing five tandem GAL4 response elements, CDDO, CDDO-Me, and CDDO-IM induce transactivation and PPAR γ interaction with multiple coactivators. A major difference among the three PPAR γ agonists was the higher activity of CDDO-Im to induce PPAR γ interactions with the corepressor SMRT. CDDO, CDDO-Me, and CDDO-Im inhibited SW-480, HCT-116, and HT-29 colon cancer cell proliferation at low concns. and induced cell death at higher concns. Growth inhibition at lower concns. correlated with induction of the tumor suppressor gene caveolin-1 which is known to inhibit colon cancer cell growth. Induction of caveolin-1 by CDDO, CDDO-Me, and CDDO-Im was inhibited by the PPAR γ antagonist N-4'-aminopyridyl-2-chloro-5-nitrobenzamide (T007), whereas higher doses induced apoptosis [poly(ADP-ribose) polymerase cleavage], which was not inhibited by T007. These results illustrate that CDDO-, CDDO-Me, and CDDO-Im induce both PPAR γ -dependent and -independent responses in colon cancer cells, and

activation of these pathways are separable and concentration-dependent for all three compds.

IT 218600-53-4

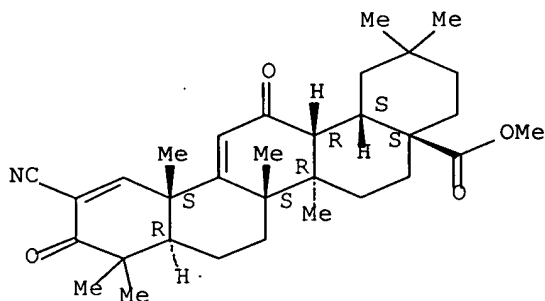
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(cyanodioxooleanadienoic acid and related compds. inhibit growth of colon cancer cells through peroxisome proliferator-activated receptor γ -dependent and -independent pathways)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:480865 CAPLUS Full-text

DOCUMENT NUMBER: 143:166163

TITLE: Triterpenoid CDDO-Im downregulates PML/RAR α expression in acute promyelocytic leukemia cells

AUTHOR(S): Ikeda, T.; Kimura, F.; Nakata, Y.; Sato, K.; Ogura, K.; Motoyoshi, K.; Sporn, M.; Kufe, D.

CORPORATE SOURCE: Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115, USA

SOURCE: Cell Death and Differentiation (2005), 12(5), 523-531
CODEN: CDDIEK; ISSN: 1350-9047

PUBLISHER: Nature Publishing Group

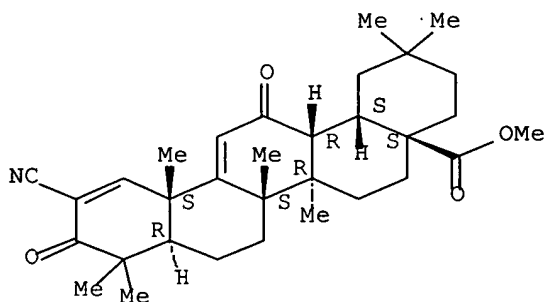
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) induces differentiation and apoptosis of diverse human tumor cells. In the present study, we examined the effects of the CDDO imidazolide imide (CDDO-lm) on the NB4 acute promyelocytic leukemia (APL) cell line and primary APL cells. The results show that CDDO-lm selectively downregulates expression of the PML/retinoic receptor alpha fusion protein by a caspase-dependent mechanism and sensitizes APL cells to the differentiating effects of all-trans retinoic acid (ATRA). CDDO-lm treatment of APL cells was also associated with disruption of redox balance and activation of the extrinsic apoptotic pathway. In concert with these results, CDDO-lm sensitizes APL cells to arsenic trioxide (ATO)-induced apoptosis. Our findings indicate that CDDO-lm may be effective in the treatment of APL by: (i) downregulation of PML/RAR α ; (ii) enhancement of ATRA-induced differentiation; and (iii) sensitization of ATO-induced APL cell death.

IT 218600-53-4
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (oleanane triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid-Me
 ester downregulated PML/RAR α fusion protein expression in human
 acute promyelocytic leukemia cell line)
 RN 218600-53-4 CAPLUS
 CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:294910 CAPLUS Full-text

DOCUMENT NUMBER: 142:441288

TITLE: Extremely potent triterpenoid inducers of the phase 2
 response: correlations of protection against oxidant
 and inflammatory stress

AUTHOR(S): Dinkova-Kostova, Albena T.; Liby, Karen T.;
 Stephenson, Katherine K.; Holtzclaw, W. David; Gao,
 Xiangqun; Suh, Nanjoo; Williams, Charlotte;
 Risingsong, Renee; Honda, Tadashi; Gribble, Gordon W.;
 Sporn, Michael B.; Talalay, Paul

CORPORATE SOURCE: The Lewis B. and Dorothy Cullman Cancer
 Chemoprotection Center, Department of Pharmacology and
 Molecular Sciences, School of Medicine, Johns Hopkins
 University, Baltimore, MD, 21205, USA

SOURCE: Proceedings of the National Academy of Sciences of the
 United States of America (2005), 102(12), 4584-4589
 CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of synthetic triterpenoid (TP) analogs of oleanolic acid are powerful
 inhibitors of cellular inflammatory processes such as the induction by IFN- γ
 of inducible nitric oxide synthase (iNOS) and of cyclooxygenase 2 in mouse
 macrophages. Here, we show that these analogs are also extremely potent
 inducers of the phase 2 response [e.g., elevation of NAD(P)H-quinone
 oxidoreductase and heme oxygenase 1], which is a major protector of cells
 against oxidative and electrophile stress. Moreover, like previously
 identified phase 2 inducers, the TP analogs use the antioxidant response
 element-Nrf2-Keap1 signaling pathway. Thus, induction of the phase 2 response

and suppression of the iNOS induction was abrogated in nrf2^{-/-} and keap1^{-/-} mouse embryonic fibroblasts. The high potency of TP analogs in inducing the phase 2 response and blocking inflammation depends on the presence of activated Michael reaction (enone) functions at critical positions in rings A and C. The most potent TP doubles NAD(P)H-quinone oxidoreductase in murine hepatoma cells at 0.28 nM and has an IC₅₀ for suppression of iNOS induction in primary mouse macrophages of 0.0035 nM. The direct interaction of this TP with thiol groups of the Keap1 sensor for inducers is demonstrated spectroscopically. The antiinflammatory and phase 2 inducer potencies of 18 TP are closely linearly correlated ($r^2 = 0.91$) over 6 orders of magnitude of concentration. Thus, in addition to blocking inflammation and promoting differentiation, these TP exhibit another very important protective property: the induction of the phase 2 response.

IT 218600-53-4

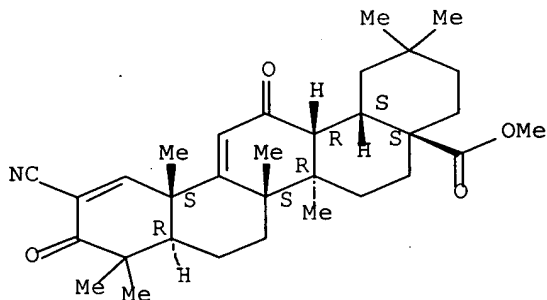
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(structure-activity relationship of extremely potent triterpenoid inducers of phase 2 response and correlations of protection against oxidant and inflammatory stress)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:670953 CAPLUS Full-text

DOCUMENT NUMBER: 141:342861

TITLE: Design, Synthesis, and Biological Evaluation of Biotin Conjugates of 2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oic Acid for the Isolation of the Protein Targets
AUTHOR(S): Honda, Tadashi; Janosik, Tomasz; Honda, Yukiko; Han, Jie; Liby, Karen T.; Williams, Charlotte R.; Couch, Robin D.; Anderson, Amy C.; Sporn, Michael B.; Gribble, Gordon W.

CORPORATE SOURCE: Department of Chemistry, Dartmouth College, Hanover, NH, 03755, USA

SOURCE: Journal of Medicinal Chemistry (2004), 47(20), 4923-4932

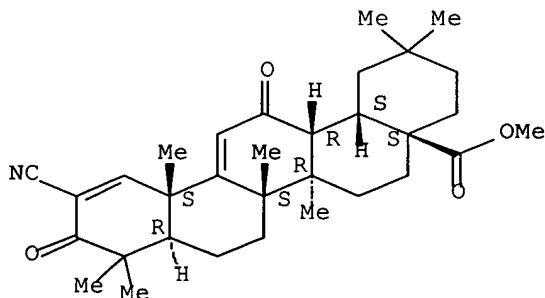
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English
 OTHER SOURCE(S): CASREACT 141:342861
 AB 2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) and related compds. [for example, CDDO-Me and CDDO-Im] are potential anti-inflammatory, cancer chemopreventive, and chemotherapeutic agents. However, the mechanisms responsible for the multiple effects of CDDO are still unclear. Clarification of these mechanisms and particularly isolation of the protein targets are essential for the development of CDDO and its analogs as clin. useful drugs. Such knowledge would provide superior opportunities for designing new compds. with improved potency and selectivity. Therefore, to isolate protein targets using affinity chromatog. with immobilized streptavidin as a carrier, we have designed and synthesized C-17 and C-23 biotin conjugates of CDDO on the basis of our established structure-activity relationships. For the synthesis of one compound, a new important precursor, 23-hydroxy-CDDO-Me was synthesized from 20 by a C-23 oxidation protocol, which involves cyclopalladation of the C-4 Me group from a 3-one oxime. The inhibitory activity of C-23 conjugate is only about 3 times less potent than the mother compound, CDDO, against the proliferation of MCF-7 breast cancer cells. Consequently, it may be a very promising tool for the isolation of the protein targets of CDDO.
 IT 218600-53-4
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (design, synthesis, and biol. evaluation of biotin conjugates of 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid for isolation of protein targets)
 RN 218600-53-4 CAPLUS
 CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 2003:832882 CAPLUS Full-text
 DOCUMENT NUMBER: 140:399426
 TITLE: Synthetic triterpenoids activate a pathway for apoptosis in AML cells involving downregulation of FLIP and sensitization to TRAIL
 AUTHOR(S): Suh, W.-S.; Kim, Y. S.; Schimmer, A. D.; Kitada, S.; Minden, M.; Andreeff, M.; Suh, N.; Sporn, M.; Reed, J. C.
 CORPORATE SOURCE: The Burnham Institute, La Jolla, CA, 92037, USA
 SOURCE: Leukemia (2003), 17(11), 2122-2129

PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Acute myelogenous leukemia (AML) remains a deadly disease for most adult patients, due primarily to the emergence of chemoresistant cells. Defects in apoptosis pathways make important contributions to chemoresistance, suggesting a need to restore apoptosis sensitivity or to identify alternative pathways for apoptosis induction. Triterpenoids represent a class of naturally occurring and synthetic compds. with demonstrated antitumor activity, including 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) and its Me ester (CDDO-m). We explored the effects of CDDO and CDDO-m in vitro on established AML cell lines (HL-60, U937, AML-2) and on freshly isolated AML blasts. CDDO and CDDO-m reduced the viability of all AML cell lines tested in a dose-dependent manner, with EDs for killing 50% of cells (ED50) within 48 h of .apprx.1 and 0.5 μ M, resp. CDDO or CDDO-m also induced substantial increases in cell death in five out of 10 samples of primary AML blasts. Cell death induced by CDDO and CDDO-m was attributed to apoptosis, based on characteristic cell morphol. and evidence of caspase activation. Immunoblot anal. demonstrated proteolytic processing of caspase-3, -7, and -8, but not caspase-9, suggesting the involvement of the extrinsic pathway, linked to apoptosis induction by TNF-family death receptors. Accordingly, CDDO and CDDO-m induced concentration-dependent redns. in the levels of FLIP protein, an endogenous antagonist of caspase-8, without altering the levels of several other apoptosis-relevant proteins. Redns. in FLIP were rapid, detectable within 3 h after exposure of AML cell lines to CDDO or CDDO-m. CDDO and CDDO-m also sensitized two of four leukemia lines to TRAIL, a TNF-family death ligand. The findings suggest that synthetic triterpenoids warrant further investigation in the treatment of AML, alone or in combination with TRAIL or other immune-based therapies.

IT 218600-53-4

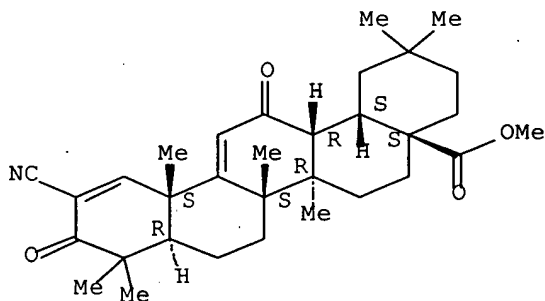
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(synthetic triterpenoids activate a pathway for apoptosis in AML cells involving downregulation of FLIP and sensitization to TRAIL)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ACCESSION NUMBER: 2003:733807 CAPLUS Full-text
 DOCUMENT NUMBER: 140:174581
 TITLE: The Novel Triterpenoid CDDO and its Derivatives Induce Apoptosis by Disruption of Intracellular Redox Balance
 AUTHOR(S): Ikeda, Takashi; Sporn, Michael; Honda, Tadashi; Gribble, Gordon W.; Kufe, Donald
 CORPORATE SOURCE: Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115, USA
 SOURCE: Cancer Research (2003), 63(17), 5551-5558
 CODEN: CNREA8; ISSN: 0008-5472
 PUBLISHER: American Association for Cancer Research
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The novel oleanane triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) induces apoptosis of human leukemia cells by activation of the extrinsic caspase-8 pathway. The mechanisms responsible for the proapoptotic effects of CDDO are unknown. The present studies demonstrate that CDDO activates the c-Jun NH2-terminal kinase and p38 mitogen-activated protein kinase in U-937 leukemia cells. The results also show that CDDO activates stress kinases by increasing levels of reactive oxygen species and decreasing intracellular glutathione (GSH) concns. Similar findings were obtained with the C-28 Me ester (CDDO-Me) and C-28 imidazolidine ester (CDDO-Im) derivs. The results also demonstrate that CDDO-induced: (a) stimulation of Jun NH2-terminal kinase; (b) activation of caspase-8; (c) loss of mitochondrial transmembrane potential; (d) release of cytochrome c; and (e) cleavage of caspase-3 are blocked by pretreatment with the antioxidant N-acetyl-L-cysteine and GSH but not with cysteine. In concert with these results, CDDO-induced apoptosis is also abrogated by N-acetyl-L-cysteine and GSH. These findings demonstrate that CDDO and its derivs. disrupt intracellular redox balance and thereby induce apoptosis.

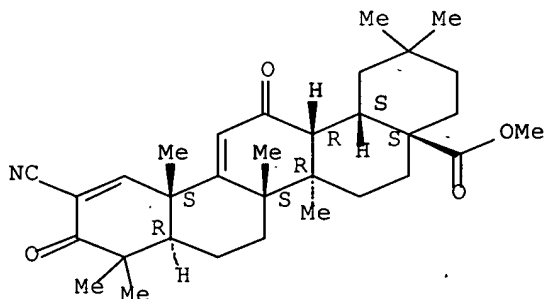
IT 218600-53-4

RL: DMA (Drug mechanism of action); BIOL (Biological study)
 (novel triterpenoid CDDO and its derivs. induce apoptosis by disruption of intracellular redox balance)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 2002:505732 CAPLUS Full-text

DOCUMENT NUMBER: 138:66283
 TITLE: An inducible pathway for degradation of FLIP protein sensitizes tumor cells to TRAIL-induced apoptosis
 AUTHOR(S): Kim, Youngsoo; Suh, Nanjoo; Sporn, Michael; Reed, John C.
 CORPORATE SOURCE: Burnham Institute, La Jolla, CA, 92037, USA
 SOURCE: Journal of Biological Chemistry (2002), 277(25), 22320-22329
 CODEN: JBCHA3; ISSN: 0021-9258
 PUBLISHER: American Society for Biochemistry and Molecular Biology
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB TRAIL (Apo2 ligand) is a member of the tumor necrosis factor (TNF) family of cytokines that induces apoptosis. Because TRAIL preferentially kills tumor cells, sparing normal tissues, interest has emerged in applying this biol. factor for cancer therapy in humans. However, not all tumors respond to TRAIL, raising questions about resistance mechanisms. We demonstrate here that a variety of natural and synthetic ligands of peroxisome proliferator-activated receptor- γ (PPAR γ) sensitize tumor but not normal cells to apoptosis induction by TRAIL. PPAR γ ligands selectively reduce levels of FLIP, an apoptosis-suppressing protein that blocks early events in TRAIL/TNF family death receptor signaling. Both PPAR γ agonists and antagonists displayed these effects, regardless of the levels of PPAR γ expression and even in the presence of a PPAR γ dominant-neg. mutant, indicating a PPAR γ -independent mechanism. Redns. in FLIP and sensitization to TRAIL-induced apoptosis were also not correlated with NF- κ B, further suggesting a novel mechanism. PPAR γ modulators induced ubiquitination and proteasome-dependent degradation of FLIP, without concomitant redns. in FLIP mRNA. The findings suggest the existence of a pharmacol. regulated novel target of this class of drugs that controls FLIP protein turnover, and raise the possibility of combining PPAR γ modulators with TRAIL for more efficacious elimination of tumor cells through apoptosis.

IT 218600-53-4

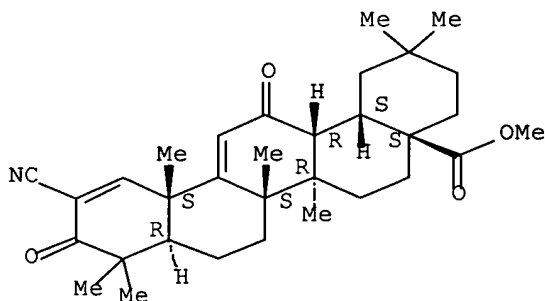
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); BIOL (Biological study); USES (Uses)

(inducible pathway for degradation of FLIP protein sensitizes tumor cells to TRAIL-induced apoptosis)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS

L5 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 2002:465747 CAPLUS Full-text
 DOCUMENT NUMBER: 137:41724
 TITLE: CDDO (2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid) compounds and combinations with other chemotherapeutics for the treatment of cancer and graft vs. host disease
 INVENTOR(S): Konopleva, Marina; Andreef, Michael; Sporn, Michael
 PATENT ASSIGNEE(S): Board of Regents, the University of Texas System, USA
 SOURCE: PCT Int. Appl., 184 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002047611	A2	20020620	WO 2001-US44541	20011128
WO 2002047611	A8	20030626		
WO 2002047611	A3	20031224		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2430454	A1	20020620	CA 2001-2430454	20011128
AU 2002043246	A5	20020624	AU 2002-43246	20011128
US 2003119732	A1	20030626	US 2001-998009	20011128
EP 1395255	A2	20040310	EP 2001-989130	20011128
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRIORITY APPLN. INFO.:			US 2000-253673P	P 20001128
			WO 2001-US44541	W 20011128

AB CDDO compds. in combination with other chemotherapeutic agents induce and potentiate cytotoxicity and apoptosis in cancer cells. One class of chemotherapeutic agents include retinoids. Cancer therapies based on these combination therapies are provided. Also provided are methods to treat graft vs. host diseases using the CDDO compds.

IT 218600-53-4

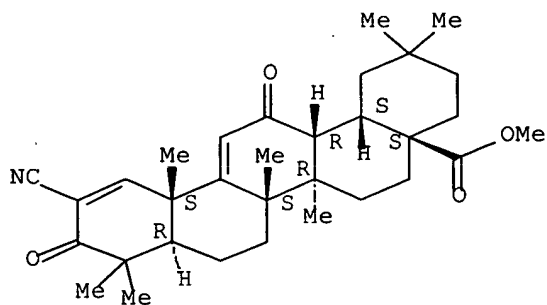
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(CDDO compds. and combinations with other chemotherapeutics for treatment of cancer and graft vs. host disease)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L5 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:211223 CAPLUS Full-text

DOCUMENT NUMBER: 137:109396

TITLE: A novel dicyanotriterpenoid, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile, active at picomolar concentrations for inhibition of nitric oxide production

AUTHOR(S): Honda, Tadashi; Honda, Yukiko; Favalaro, Frank G.; Gribble, Gordon W.; Suh, Nanjoo; Place, Andrew E.; Rendi, Mara H.; Sporn, Michael B.

CORPORATE SOURCE: Department of Chemistry, Dartmouth College, Hanover, NH, 03755, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (2002), 12(7), 1027-1030

CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 137:109396

AB New oleanane triterpenoids with various substituents at the C-17 position of 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) and Me 2-carboxy-3,12-dioxooleana-1,9(11)-dien-28-oate were synthesized. Among them, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile shows extremely high inhibitory activity (IC₅₀ = 1 pM level) against production of nitric oxide induced by interferon- γ in mouse macrophages. This potency is about 100 times and 30 times more potent than CDDO and dexamethasone, resp.

IT 218600-53-4P

RL: BSU (Biological study, unclassified); SPN (Synthetic preparation);

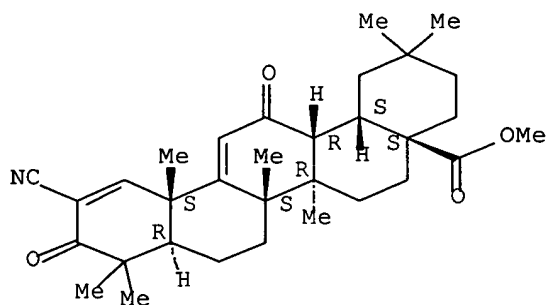
BIOL (Biological study); PREP (Preparation)

(preparation of dicyanotriterpenoids and their inhibitory activity against production of nitric oxide induced by interferon- γ in mouse macrophages)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:95270 CAPLUS Full-text

DOCUMENT NUMBER: 136:379616

TITLE: Identification of a novel synthetic triterpenoid, methyl-2-cyano-3,12-dioxooleana-1,9-dien-28-oate, that potently induces caspase-mediated apoptosis in human lung cancer cells

AUTHOR(S): Kim, Kevin B.; Lotan, Reuben; Yue, Ping; Sporn, Michael B.; Suh, Nanjoo; Gribble, Gordon W.; Honda, Tadashi; Wu, Gen Sheng; Hong, Waun Ki; Sun, Shi-Yong

CORPORATE SOURCE: Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA

SOURCE: Molecular Cancer Therapeutics (2002), 1(3), 177-184
CODEN: MCTOCF; ISSN: 1535-7163

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Lung cancer continues to be the leading cause of cancer-related death in the United States. Therefore, new agents targeting prevention and treatment of lung cancer are urgently needed. In the present study, we demonstrate that a novel synthetic triterpenoid methyl-2-cyano-3,12-dioxooleana-1,9-dien-28-oate (CDDO-Me) is a potent inducer of apoptosis in human non-small cell lung carcinoma (NSCLC) cells. The concns. required for a 50% decrease in cell survival (IC50) ranged from 0.1 to 0.3 μ M. CDDO-Me induced rapid apoptosis and triggered a series of effects associated with apoptosis including a rapid release of cytochrome c from mitochondria, activation of procaspase-9, -7, -6, and -3, and cleavage of poly(ADP-ribose) polymerase and lamin A/C. Moreover, the caspase-3 inhibitor Z-DEVD-FMK and the pan caspase inhibitor Z-VAD-FMK suppressed CDDO-Me-induced apoptosis. These results indicate that CDDO-Me induced apoptosis in human NSCLC cells via a cytochrome c-triggered caspase activation pathway. CDDO-Me did not alter the level of Bcl-2 and Bcl-xL proteins, and no correlation was found between cell sensitivity to CDDO-Me and basal Bcl-2 expression level. Furthermore, overexpression of Bcl-2 did not protect cells from CDDO-Me-induced apoptosis. These results suggest that CDDO-Me induces apoptosis in NSCLC cells irresp. of Bcl-2 expression level. In addition, no correlation was found between cell sensitivity to CDDO-Me and p53 status, suggesting that CDDO-Me induce a p53-independent apoptosis. Our results demonstrate that CDDO-Me may be a good candidate for addnl. evaluation as a potential therapeutic agent for human lung cancers and possibly other types of cancer.

IT 218600-53-4

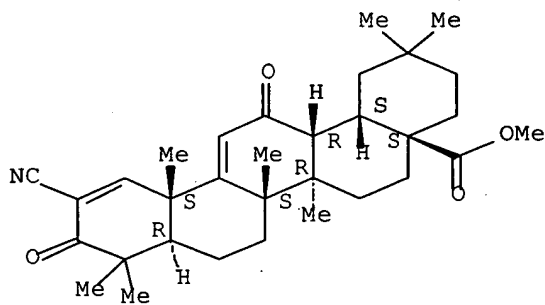
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(identification of a novel synthetic triterpenoid, Me-2-cyano-3,12-
dioxooleana-1,9-dien-28-oate, that potently induces caspase-mediated
apoptosis in human lung cancer cells)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:29939 CAPLUS Full-text

DOCUMENT NUMBER: 136:318974

TITLE: Novel triterpenoid CDDO-Me is a potent inducer of
apoptosis and differentiation in acute myelogenous
leukemia

AUTHOR(S): Konopleva, Marina; Tsao, Tzee; Ruvolo, Peter; Stiouf,
Irina; Estrov, Zeev; Leysath, Clinton E.; Zhao,
Shourong; Harris, David; Chang, Shirong; Jackson, C.
Ellen; Munsell, Mark; Suh, Nanjoo; Gribble, Gordon;
Honda, Tadashi; May, W. Stratford; Sporn, Michael B.;
Andreeff, Michael

CORPORATE SOURCE: Department of Blood and Marrow Transplantation,
Section of Molecular Hematology and Therapy, The
University of Texas M. D. Anderson Cancer Center,
Houston, TX, 77030, USA

SOURCE: Blood (2002), 99(1), 326-335
CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: American Society of Hematology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oleic acid
(CDDO) inhibits proliferation and induces differentiation and apoptosis in
myeloid leukemia cells. This work studied the effects of the C-28 Me ester of
CDDO, CDDO-Me, on cell growth and apoptosis of leukemic cell lines and primary
acute myelogenous leukemia (AML). CDDO-Me decreased the viability of leukemic
cell lines, including multidrug resistant (MDR)-1-overexpressing, p53null HL-
60-Dox and primary AML cells, and it was 3-5-fold more active than CDDO.
CDDO-Me induced a loss of mitochondrial membrane potential, induced caspase-3
cleavage, and increased annexin V binding and DNA fragmentation, suggesting
the induction of apoptosis. CDDO-Me induced the proapoptotic Bax protein that

precedes caspase activation. Furthermore, CDDO-Me inhibited the activation of ERK1/2, as determined by the inhibition of mitochondrial ERK1/2 phosphorylation, and it blocked Bcl-2 phosphorylation, rendering Bcl-2 less antiapoptotic. CDDO-Me induced granulo-monocytic differentiation in HL-60 cells and monocytic differentiation in primary cells. Colony formation of AML progenitors was inhibited in a concentration-dependent fashion, whereas normal CD34+ progenitor cells were less affected. Combinations with all-trans-retinoic acid or the retinoic acid receptor-specific ligand LG100268 enhanced the effects of CDDO-Me on the cell viability and terminal differentiation of myeloid leukemic cell lines. In conclusion, CDDO-Me is an MDR-1- and a p53-independent compound that exerts strong antiproliferative, apoptotic, and differentiating effects in myeloid leukemic cell lines and in primary AML samples when used in submicromolar concns. The differential effects of CDDO-Me on leukemic and normal progenitor cells suggest that CDDO-Me has potential as a novel compound in the treatment of hematol. malignancies.

IT 218600-53-4

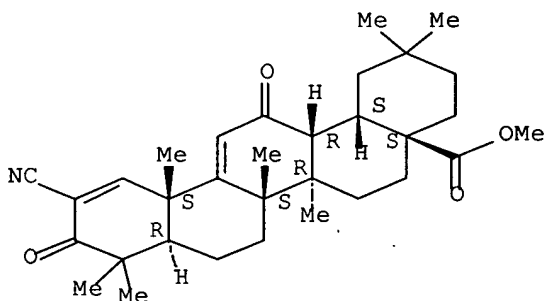
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(triterpenoid CDDO-Me induction of apoptosis and differentiation in acute myelogenous leukemia)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:702718 CAPLUS Full-text

DOCUMENT NUMBER: 134:274

TITLE: A synthetic triterpenoid, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO), is a ligand for the peroxisome proliferator-activated receptor γ

AUTHOR(S): Wang, Yongping; Porter, Weston W.; Suh, Nanjoo; Honda, Tadashi; Gribble, Gordon W.; Leesnitzer, Lisa M.; Plunket, Kelli D.; Mangelsdorf, David J.; Blanchard, Steven G.; Willson, Timothy M.; Sporn, Michael B.

CORPORATE SOURCE: Department of Pharmacology, Dartmouth Medical School and Dartmouth College, Hanover, NH, 03755, USA

SOURCE: Molecular Endocrinology (2000), 14(10), 1550-1556

CODEN: MOENEN; ISSN: 0888-8809

PUBLISHER: Endocrine Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A novel synthetic triterpenoid, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO), previously reported to have potent differentiating, antiproliferative, and antiinflammatory activities, has been identified as a ligand for the peroxisome proliferator-activated receptor γ (PPAR γ). CDDO induces adipocytic differentiation in 3T3-L1 cells, although it is not as potent as the full agonist of PPAR γ , rosiglitazone. Binding studies of CDDO to PPAR γ using a scintillation proximity assay give a K_i between 10^{-8} to 10^{-7} M. In transactivation assays, CDDO is a partial agonist for PPAR γ . The Me ester of CDDO, CDDO-Me, binds to PPAR γ with similar affinity, but is an antagonist. Like other PPAR γ ligands, CDDO synergizes with a retinoid X receptor (RXR)-specific ligand to induce 3T3-L1 differentiation, while CDDO-Me is an antagonist in this assay. The partial agonism of CDDO and the antagonism of CDDO-Me reflect the differences in their capacity to recruit or displace cofactors of transcriptional regulation; CDDO and rosiglitazone both release the nuclear receptor corepressor, NCoR, from PPAR γ , while CDDO-Me does not. The differences between CDDO and rosiglitazone as either partial or full agonists, resp., are seen in the weaker ability of CDDO to recruit the coactivator CREB-binding protein, CBP, to PPAR γ . Our results establish the triterpenoid CDDO as a member of a new class of PPAR γ ligands.

IT 218600-53-4

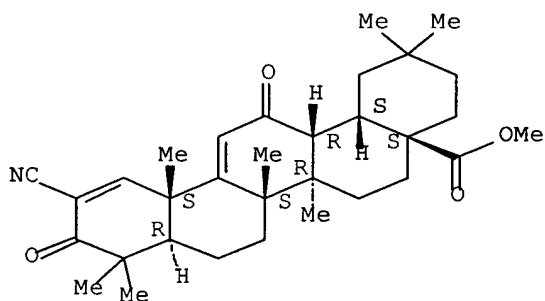
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(synthetic triterpenoid, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO): ligand for PPAR γ)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:632697 CAPLUS Full-text

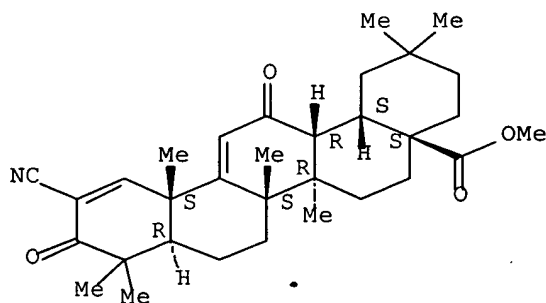
DOCUMENT NUMBER: 133:350364

TITLE: Synthetic Oleanane and Ursane Triterpenoids with Modified Rings A and C: A Series of Highly Active Inhibitors of Nitric Oxide Production in Mouse Macrophages

AUTHOR(S): Honda, Tadashi; Rounds, BarbieAnn V.; Bore, Lothar; Finlay, Heather J.; Favalaro, Frank G., Jr.; Suh, Nanjoo; Wang, Yongping; Sporn, Michael B.; Gribble,

CORPORATE SOURCE: Gordon W.
 Department of Chemistry, Dartmouth College Dartmouth
 Medical School, Hanover, NH, 03755, USA
 SOURCE: Journal of Medicinal Chemistry (2000), 43(22),
 4233-4246
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 133:350364
 AB New olean- and urs-1-en-3-one triterpenoids with various modified rings C have
 been synthesized as potential antiinflammatory and cancer chemopreventive
 agents and evaluated for their inhibitory activities against production of
 nitric oxide induced by interferon- γ in mouse macrophages. These studies
 revealed that 9(11)-en-12-one and 12-en-11-one functionalities in ring C
 increase the potency by about 2-10 times compared with the original 12-ene.
 Subsequently, novel olean- and urs-1-en-3-one derivs. with nitrile and
 carboxyl groups at C-2 in ring A and with 9(11)-en-12-one and 12-en-11-one
 functionalities in ring C were synthesized. Among them, Me 2-cyano-3, 12-
 dioxooleana-1,9(11)-dien-28- oate, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-
 oic acid (CDDO) (I), and Me 2-carboxy-3,12-dioxooleana-1,9(11)-dien-28-oate
 were found to have extremely high potency (IC₅₀ = 0.1 nM level). Their
 potency is similar to that of dexamethasone although they do not act through
 the glucocorticoid receptor. Overall, the combination of modified rings A and
 C increases the potency by about 10 000 times compared with the lead compound,
 3-oxooleana-1,12-dien-28-oic acid (IC₅₀ = 1 μ M level). The selected oleanane
 triterpenoid, I, was found to be a potent, multifunctional agent in various in
 vitro assays and to show antiinflammatory activity against thioglycollate-
 interferon- γ -induced mouse peritonitis.
 IT 218600-53-4P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL
 (Biological study); PREP (Preparation); RACT (Reactant or reagent)
 (synthetic oleanane and ursane triterpenoids, a series of highly active
 inhibitors of nitric oxide production in mouse macrophages)
 RN 218600-53-4 CAPLUS
 CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ACCESSION NUMBER: 1999:811070 CAPLUS Full-text
 DOCUMENT NUMBER: 132:44971
 TITLE: Therapeutic triterpenoid compositions and methods of use for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases
 INVENTOR(S): Gribble, Gordon W.; Honda, Tadashi; Sporn, Michael B.; Suh, Nanjoo
 PATENT ASSIGNEE(S): Trustees of Dartmouth College, USA
 SOURCE: PCT Int. Appl., 49 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9965478	A1	19991223	WO 1999-US13635	19990618
W: CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6326507	B1	20011204	US 1999-335003	19990617
CA 2335505	A1	19991223	CA 1999-2335505	19990618
EP 1089724	A1	20010411	EP 1999-928731	19990618
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002530272	T	20020917	JP 2000-554358	19990618
US 2002042535	A1	20020411	US 2001-927081	20010809
US 6552075	B2	20030422		
US 2003236303	A1	20031225	US 2003-395372	20030324
US 2005288363	A1	20051229	US 2005-121316	20050503
PRIORITY APPLN. INFO.:				
			US 1998-90053P	P 19980619
			US 1999-335003	A 19990617
			WO 1999-US13635	W 19990618
			US 2001-927081	A1 20010809
			US 2003-395372	A1 20030324

OTHER SOURCE(S): MARPAT 132:44971

AB Triterpenoid compds., e.g. 2-cyano-3,12-dioxoolean-1,9-dien--28-oic acid, and methods are disclosed which are useful for chemopreventative treatment of diseases such as cancer, Alzheimer's disease, Parkinson's disease, inflammatory bowel diseases, and multiple sclerosis.

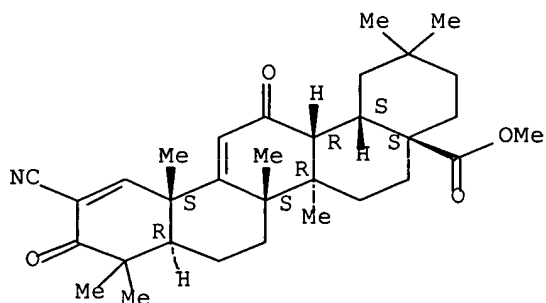
IT 218600-53-4

RL: RCT (Reactant); RACT (Reactant or reagent)
 (reaction; triterpenoids for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 25 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:709911 CAPLUS Full-text

DOCUMENT NUMBER: 130:75734

TITLE: Design and synthesis of 2-cyano-3,12-dioxolean-1,9-dien-28-oic acid, a novel and highly active inhibitor of nitric oxide production in mouse macrophages

AUTHOR(S): Honda, Tadashi; Rounds, BarbieAnn V.; Gribble, Gordon W.; Suh, Nanjoo; Wang, Yongping; Sporn, Michael B.

CORPORATE SOURCE: Department of Chemistry, Dartmouth College, Hanover, NH, 03755, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (1998), 8(19), 2711-2714

CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 130:75734

AB New derivs. with electron-withdrawing substituents at the C-2 position of 3-oxoolean-1-en-28-oic acid were synthesized. Among them, 2-cyano-3,12-dioxolean-1,9-dien-28-oic acid (CDDO) was 400 times more potent than previous compds. the authors have made as an inhibitor of production of nitric oxide induced by interferon- γ in mouse macrophages (IC₅₀, 0.4 nM). Structure-activity relations are discussed. The potency of CDDO was similar to that of dexamethasone, although CDDO does not act through the glucocorticoid receptor.

IT 218600-53-4P

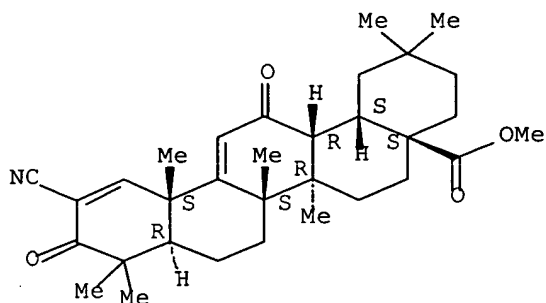
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; design and synthesis of 2-cyanodioxooleanoic acid as novel and highly active inhibitor of nitric oxide production in mouse macrophages in relation to structure)

RN 218600-53-4 CAPLUS

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 25 USPATFULL on STN

ACCESSION NUMBER: 2005:331377 USPATFULL Full-text

TITLE: Therapeutic compositions and methods of use

INVENTOR(S): Gribble, Gordon W., Norwich, VT, UNITED STATES

Honda, Tadashi, Hanover, NH, UNITED STATES

Sporn, Michael B., Tunbridge, VT, UNITED STATES

Suh, Nanjoo, Hanover, NH, UNITED STATES

PATENT ASSIGNEE(S): Trustees of Dartmouth College (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005288363	A1	20051229
APPLICATION INFO.:	US 2005-121316	A1	20050503 (11)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2003-395372, filed on 24 Mar 2003, PENDING		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	FULBRIGHT & JAWORSKI L.L.P., 600 CONGRESS AVE., SUITE 2400, AUSTIN, TX, 78701, US		
NUMBER OF CLAIMS:	15		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	11 Drawing Page(s)		
LINE COUNT:	931		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds and methods useful for chemopreventative treatment of diseases such as cancer, Alzheimer's disease, Parkinson's disease, inflammatory bowel diseases, and multiple sclerosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

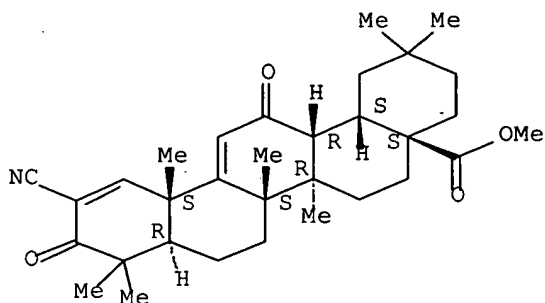
IT 218600-53-4

(reaction; triterpenoids for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases)

RN 218600-53-4 USPATFULL

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L5 ANSWER 22 OF 25 USPATFULL on STN

ACCESSION NUMBER: 2003:335425 USPATFULL Full-text
 TITLE: Therapeutic compositions and methods of use
 INVENTOR(S): Gribble, Gordon W., Norwich, VT, UNITED STATES
 Honda, Tadashi, Hanover, NH, UNITED STATES
 Sporn, Michael B., Tunbridge, VT, UNITED STATES
 Suh, Nanjoo, Hanover, NH, UNITED STATES
 PATENT ASSIGNEE(S): Trustees of Dartmouth College (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003236303	A1	20031225
APPLICATION INFO.:	US 2003-395372	A1	20030324 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2001-927081, filed on 9 Aug 2001, GRANTED, Pat. No. US 6552075 Division of Ser. No. US 1999-335003, filed on 17 Jun 1999, GRANTED, Pat. No. US 6326507		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-90053P	19980619 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Steven L. Highlander, Esq., FULBRIGHT & JAWORSKI L.L.P., Suite 2400, 600 Congress Avenue, Austin, TX, 78701	
NUMBER OF CLAIMS:	73	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	14 Drawing Page(s)	
LINE COUNT:	1146	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds and methods useful for chemopreventative treatment of diseases such as cancer, Alzheimer's disease, Parkinson's disease, inflammatory bowel diseases, and multiple sclerosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

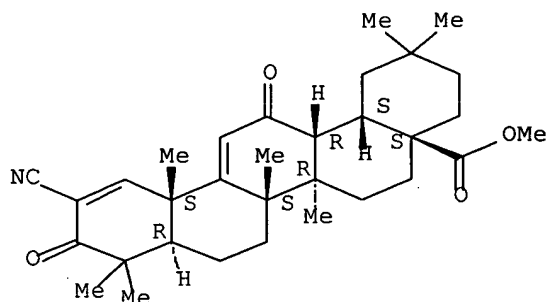
IT 218600-53-4

(reaction; triterpenoids for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases)

RN 218600-53-4 USPATFULL

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L5 ANSWER 23 OF 25 USPATFULL on STN

ACCESSION NUMBER: 2003:173884 USPATFULL Full-text
TITLE: CDDO-compounds and combination therapies thereof
INVENTOR(S): Konopleva, Marina, Houston, TX, UNITED STATES
Andreeff, Michael, Houston, TX, UNITED STATES
Sporn, Michael B., Tunbridge, VT, UNITED STATES
PATENT ASSIGNEE(S): Board of (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003119732	A1	20030626
APPLICATION INFO.:	US 2001-998009	A1	20011128 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-253673P	20001128 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Priya D. Subramony, Fulbright & Jaworski L.L.P., 600 Congress Avenue, Suite 2400, Austin, TX, 78701	
NUMBER OF CLAIMS:	79	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	35 Drawing Page(s)	
LINE COUNT:	5276	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB CDDO-compounds in combination with other chemotherapeutic agents induce and potentiate cytotoxicity and apoptosis in cancer cell. One class of chemotherapeutic agents include retinoids. Cancer therapies based on these combination therapies are provided. Also provided are methods to treat graft versus host diseases using the CDDO compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

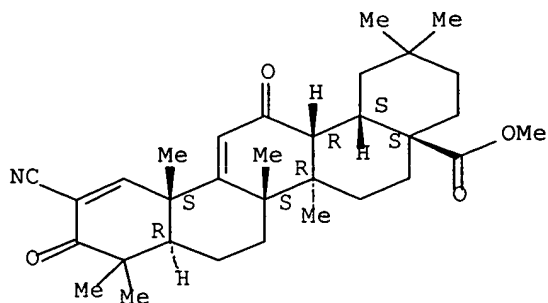
IT 218600-53-4

(CDDO compds. and combinations with other chemotherapeutics for treatment of cancer and graft vs. host disease)

RN 218600-53-4 USPATFULL

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L5 ANSWER 24 OF 25 USPATFULL on STN

ACCESSION NUMBER: 2002:78876 USPATFULL Full-text

TITLE: Therapeutic compounds and methods of use

INVENTOR(S): Gribble, Gordon W., Norwich, VT, UNITED STATES

Honda, Tadashi, Hanover, NH, UNITED STATES

Sporn, Michael B., Tunbridge, VT, UNITED STATES

Suh, Nanjoo, Hanover, NH, UNITED STATES

PATENT ASSIGNEE(S): Trustees of Dartmouth College (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002042535	A1	20020411
	US 6552075	B2	20030422
APPLICATION INFO.:	US 2001-927081	A1	20010809 (9)
RELATED APPLN. INFO.:	Division of Ser. No. US 1999-335003, filed on 17 Jun 1999, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-90053P	19980619 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Steven L. Highlander, FULBRIGHT & JAWORSKI L.L.P., Suite 2400, 600 Congress Avenue, Austin, TX, 78701	
NUMBER OF CLAIMS:	73	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	11 Drawing Page(s)	
LINE COUNT:	1150	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds and methods useful for chemopreventative treatment of diseases such as cancer, Alzheimer's disease, Parkinson's disease, inflammatory bowel diseases, and multiple sclerosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

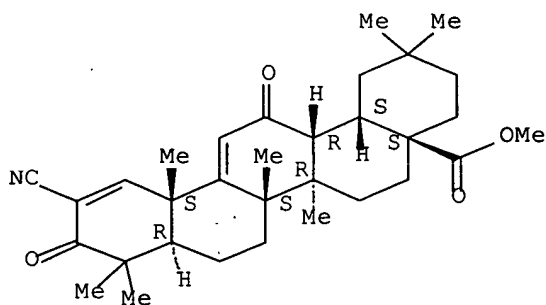
IT 218600-53-4

(reaction; triterpenoids for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases)

RN 218600-53-4 USPATFULL

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L5 ANSWER 25 OF 25 USPATFULL on STN

ACCESSION NUMBER: 2001:221178 USPATFULL Full-text

TITLE: Therapeutic compounds and methods of use

INVENTOR(S): Gribble, Gordon W., Norwich, VT, United States

Honda, Tadashi, Hanover, NH, United States

Sporn, Michael B., Tunbridge, VT, United States

Suh, Nanjoo, Hanover, NH, United States

PATENT ASSIGNEE(S): Trustees of Dartmouth College, Hanover, NH, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6326507	B1	20011204
APPLICATION INFO.:	US 1999-335003		19990617 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-90053P	19980619 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Higel, Floyd D.	
ASSISTANT EXAMINER:	Sackey, Ebenezer	
LEGAL REPRESENTATIVE:	Fulbright & Jaworski, LLP	
NUMBER OF CLAIMS:	13	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	14 Drawing Figure(s); 11 Drawing Page(s)	
LINE COUNT:	964	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds and methods useful for chemopreventative treatment of diseases such as cancer, Alzheimer's disease, Parkinson's disease, inflammatory bowel diseases, and multiple sclerosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

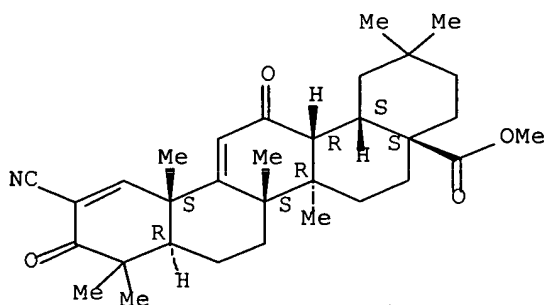
IT 218600-53-4

(reaction; triterpenoids for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases)

RN 218600-53-4 USPATFULL

CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



=> s 15 and (cancer or tumor or proliferation)

L7 19 L5 AND (CANCER OR TUMOR OR PROLIFERATION)

=> d his

(FILE 'HOME' ENTERED AT 17:02:22 ON 13 MAR 2007)

FILE 'REGISTRY' ENTERED AT 17:03:03 ON 13 MAR 2007

L1 STRUCTURE UPLOADED

L2 1 S L1 EXA FULL

L3 STRUCTURE UPLOADED

L4 1 S L3 EXA FULL

FILE 'MEDLINE, CAPLUS, WPIDS, USPATFULL' ENTERED AT 17:06:49 ON 13 MAR 2007

L5 25 S L4

L6 3 S L5 NOT PY>2000

L7 19 S L5 AND (CANCER OR TUMOR OR PROLIFERATION)

=>

---Logging off of STN---

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Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	165.58	287.99
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-17.94	-17.94

STN INTERNATIONAL LOGOFF AT 17:09:16 ON 13 MAR 2007